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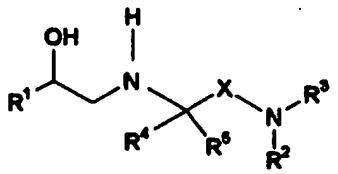
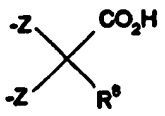
(54) Title: PHENETHANOLAMINE DERIVATIVES AND THEIR USE AS ATYPICAL BETA-ADRENOCEPTOR AGONISTS

(57) Abstract

The present invention relates to phenethanolamine derivatives of formula (I), wherein: R^1 represents an aryl group optionally substituted by one or more substituents selected from halo, hydroxy, C_{1-6}alkoxy, C_{1-6}alkyl, nitro, cyano, hydroxymethyl and trifluoromethyl; R^2 represents H or C_{1-6}alkyl; R^3 represents a phenyl or heteroaryl group substituted by R^6 and R^7; R^4 and R^5 each independently represent H or C_{1-6}alkyl or, R^4 and R^5 together form a C_{3-6}cycloalkyl group; R^6 represents ZCH_2CO_2H and R^7 represents H or ZCH_2CO_2H, or R^6 and R^7 together represent a group (a), wherein each Z may be the same or different and is selected from a bond, CH_2, O, S or NR^9, R^8 is H or CO_2H and R^9 is H or C_{1-6}alkyl; X represents$(CH_2)_n$ where n is 1 or 2; and pharmaceutically acceptable derivatives thereof; to processes for their preparation; and their use in the treatment of conditions susceptible of amelioration by an atypical beta-adrenoceptor agonist.



(I)



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PHENETHANOLAMINE DERIVATIVES AND THEIR USE AS ATYPICAL BETA-ADRENOCEPTOR AGONISTS

This invention relates to a new class of chemical compounds and to their use in medicine. In particular, the invention concerns novel phenethanolamine derivatives, methods for their preparation, pharmaceutical compositions containing them and their use as agonists at atypical beta-adrenoceptors (also known as beta-3-adrenoceptors). Such receptors have been described for example by J R S Arch *et. al.*, *Nature*, 309, 163-165 (1984); C Wilson *et. al.*, *Eur. J. Pharmacol.*, 100, 309-319 (1984); L J Emorine *et. al.*, *Science*, 245, 1118-1121 (1989); and A. Bianchetti *et. al. Br. J. Pharmacol.*, 100, 831-839 (1990). Phenethanolamine derivatives having activity at atypical beta-adrenoceptors are disclosed in, for example, European Patent Applications EP-A-0455006 and EP-A-0543662.

Atypical beta-adrenoceptors belong to the family of adrenoceptors which mediate the physiological actions of the hormones adrenaline and noradrenaline. Sub-types of the adrenoceptors, α_1 -, α_2-, β_1-, β_2- and β_3- (atypical) can be identified on the basis of their pharmacological properties and physiological effects. Chemical agents which stimulate or block these receptors (but not β_3) are widely used in clinical medicine. More recently, emphasis has been placed upon specific receptor selectivity in order to reduce side effects caused, in part, by interactions with other receptors.

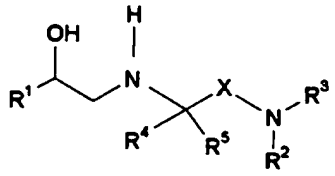
Atypical beta-adrenoceptors are known to occur in adipose tissue and the gastrointestinal tract.

Atypical beta-adrenoceptor agonists have been found to be particularly useful as thermogenic anti-obesity agents and as anti-diabetic agents. Compounds having atypical beta-adrenoceptor agonist activity have also been described as being useful in the treatment of hyperglycaemia, as animal growth promoters, as blood platelet aggregation inhibitors, as

positive inotropic agents and as antiatherosclerotic agents, and as being useful in the treatment of glaucoma.

We have now found a novel class of phenylethanolamine derivatives which act as agonists at atypical beta-adrenoceptors.

The invention therefore provides, in a first aspect, compounds of formula (I):



(I)

wherein

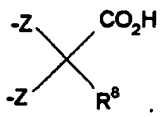
R^1 represents an aryl group optionally substituted by one or more substituents selected from halo, hydroxy, C_{1-6}alkoxy, C_{1-6}alkyl, nitro, cyano, hydroxymethyl and trifluoromethyl;

R^2 represents H or C_{1-6}alkyl;

R^3 represents a phenyl or heteroaryl group substituted by R^6 and R^7;

R^4 and R^5 each independently represent H or C_{1-6}alkyl or, R^4 and R^5 together form a C_{3-6} cycloalkyl group;

R^6 represents ZCH_2CO_2H and R^7 represents H or ZCH_2CO_2H, or R^6 and R^7 together represent a group



wherein each Z may be the same or different and is selected from a bond, CH_2, O, S or NR^9;

R^8 is H or CO_2H;

R^9 is H or C_{1-6}alkyl;

X represents $(CH_2)_n$ where n is 1 or 2;

and physiologically acceptable derivatives thereof.

Referring to the general formula (I), alkyl includes both straight and branched chain saturated hydrocarbon groups. Similarly, alkoxy includes both straight and branched chain groups.

Referring to the general formula (I), aryl includes monocyclic or bicyclic aromatic carbocyclic groups such as phenyl and naphthyl.

Referring to the general formula (I), heteroaryl includes 5 or 6 membered aromatic heterocyclic rings containing one or more, e.g. 1, 2 or 3, nitrogen atoms and optionally a sulphur or an oxygen atom. Examples of such groups include imidazole, thiazole, oxazole, triazole, pyrazine, pyrimidine, pyridazine, pyridine, pyrazole, isoxazole, isothiazole, furan, thiophene and pyrrole.

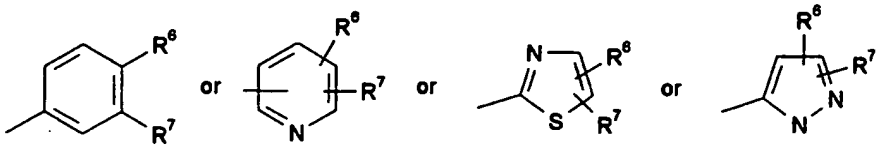
Referring to the general formula (I), when R^3 represents a heteroaryl group as defined above, this may be attached to the nitrogen atom via any vacant carbon atom of the heterocycle. For example, when R^3 represents pyridine, the pyridine ring may be attached via the ortho, meta or para position, preferably the meta-position.

Preferably R^1 represents phenyl optionally substituted by one, two or three substituents selected from halo, hydroxy, C_{1-6}alkoxy, C_{1-6}alkyl, nitro, cyano, hydroxymethyl and trifluoromethyl. More preferably R^1 represents phenyl substituted by a chlorine, fluorine or bromine atom or a methyl or trifluoromethyl group, which atom or group is preferably located in the meta

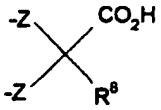
position. Most preferably R^1 represents phenyl substituted by a chlorine atom located in the meta position.

Preferably R^2 represents H or C_{1-6}alkyl such as methyl, ethyl, i-propyl or n-propyl. More preferably R^2 represents methyl or, more preferably, H.

Preferably R^3 represents a group

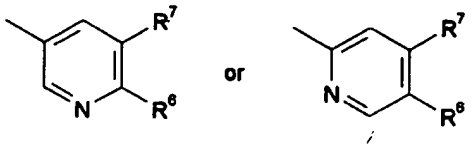


wherein R^6 and R^7 are as previously defined, more preferably R^6 represents ZCH_2CO_2H and R^7 represents H, or R^6 and R^7 represent a group



where both Z's represent O and R^8 is H

Preferably, when R^3 contains a pyridyl group, this is

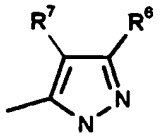


wherein R^6 and R^7 are as previously defined, more preferably R^6 represents ZCH_2CO_2H and R^7 represents H.

Preferably, when R^3 contains a thiazole group,this is

wherein R^6 and R^7 are as previously defined, more preferably R^6 represents ZCH_2CO_2H and R^7 represents H.

Preferably, when R^3 contains a pyrazole group,this is



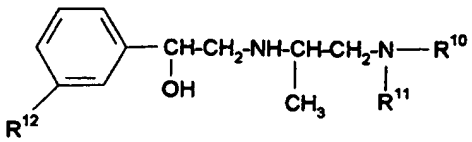
wherein R^6 and R^7 are as previously defined, more preferably R^6 represents ZCH_2CO_2H and R^7 represents H.

Where R^4 and R^5 are a cycloalkyl group, cyclopropyl is preferred.

Preferably one of R^4 and R^5 represents C_{1-6}alkyl, such as methyl, or i-propyl, more preferably methyl, and the other represents H. Also preferred are compounds where R^4 and R^5 are H.

Preferably X represents CH_2.

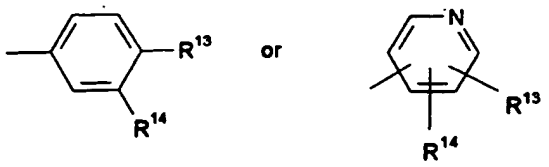
A preferred sub-class of the compounds of the general formula (I) is that defined by formula (II)



(II)

wherein

R^{10} represents



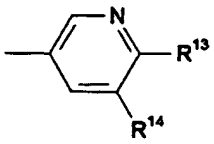
R^{11} represents H or C_{1-6}alkyl;

R^{12} represents a chlorine, fluorine or bromine atom or a methyl or trifluoromethyl group;

one of R^{13} and R^{14} represents H and the other of R^{13} and R^{14} represents CH_2CO_2H, $(CH_2)_2CO_2H$ or OCH_2CO_2H;

and physiologically acceptable derivatives thereof.

A preferred sub-class of compounds of formula (II) are those wherein R^{10} represents



where R^{13} and R^{14} are as defined above.

It will be appreciated that the above compounds of formulae (I) and (II) are optically active. The individual, isolated isomers and mixtures thereof, including racemates, are within the scope of the present invention. Particularly preferred compounds of formula (II) are those wherein the asymmetric carbon atoms in the -CH(OH)- group and the $-CH(CH_3)-$ group are in the (R)-configuration.

Suitable compounds of general formula (I) for use according to the invention are:

[4-({2R-[2-(3-Chlorophenyl)-2R-hydroxy-ethylamino]-propyl}-methyl-amino)-phenyl]-acetic acid;

(3-{2R-[2-(3-Chlorophenyl)-2R-hydroxy-ethylamino]-propylamino}-phenyl)-acetic acid;

(4-{2R-[2-(3-Chlorophenyl)-2R-hydroxy-ethylamino]-2-methyl-propylamino}-phenyl)-acetic acid;

[4-({1-[2-(3-Chlorophenyl)-2R-hydroxy-ethylamino]-cyclopropylmethyl}-amino)-phenyl]-acetic acid;

(4-{2R-[2-(3-Chlorophenyl)-2R-hydroxy-ethylamino]-3-methyl-butylamino}-phenyl)-acetic acid;

[4-({2R-[2-(3-Chlorophenyl)-2R-hydroxy-ethyl]-methyl-amino)-phenyl]-acetic acid;

[5-({1-[2-(3-Chlorophenyl)-2R-hydroxy-ethylamino]-cyclopropylmethyl}-amino)-pyridin-2-yl]-acetic acid;

(2-{2R-[2-(3-Chlorophenyl)-2R-hydroxy-ethylamino]-propylamino}-thiazol-4-yl)-acetic acid;

5-{2R-[2-(3-Chlorophenyl)-2R-hydroxy-ethylamino]-propylamino}-benzo[1,3]dioxole-2-carboxylic acid;

(5-{2-[2-(3-Chlorophenyl)-2R-hydroxy-ethylamino]-ethylamino}-pyridin-2-yl)-acetic acid;

(6-{2R-[2-(3-Chlorophenyl)-2R-hydroxy-ethylamino]-propylamino}-pyridin-3-yl)-acetic acid;

(5-{2R-[2-(3-Chlorophenyl)-2R-hydroxy-ethylamino]-propylamino}-pyrazol-3-yl)-acetic acid;

or a physiologically acceptable derivative thereof.

Particularly preferred compounds of general formula (I) for use according to the present invention are:

(4-[2R-[2-(3-chlorophenyl)-2R-hydroxy-ethylamino]propylamino]-phenyl)-acetic acid;

(5-{2R-[2-(3-Chlorophenyl)-2R-hydroxy-ethylamino]-propylamino}-pyridin-2-yl)-acetic acid;

(4-{2-[2-(3-Chlorophenyl)-2R-hydroxy-ethylamino]-ethylamino}-phenyl)-acetic acid;

or a physiologically acceptable derivative thereof.

By "a physiologically acceptable derivative" is meant any physiologically acceptable salt, ester, or salt of such ester, of a compound of formula (I) or

any other compound which, upon administration to the recipient, is capable of providing (directly or indirectly) a compound of formula (I) or an active metabolite or residue thereof.

It will be appreciated by those skilled in the art that the compounds of formula (I) may be modified to provide physiologically acceptable derivatives thereof at any of the functional groups in the compounds of formula (I). Of particular interest as such derivatives are compounds modified at the carboxyl function, hydroxyl functions or at amino groups.

It will be appreciated by those skilled in the art that the physiologically acceptable derivatives of the compounds of formula (I) may be derivatised at more than one position.

Preferred pharmaceutically acceptable derivatives of the compounds of formula (I) are physiologically acceptable salts thereof.

Physiologically acceptable salts of the compounds of formula (I) include those derived from physiologically acceptable inorganic and organic acids and bases. Examples of suitable acids include hydrochloric, hydrobromic, sulphuric, nitric, perchloric, fumaric, maleic, phosphoric, glycollic, lactic, salicylic, succinic, toluene- p-sulphonic, tartaric, acetic, citric, methanesulphonic, formic, benzoic, malonic, naphthalene-2-sulphonic and benzenesulphonic acids. Other acids such as oxalic, while not in themselves physiologically acceptable may be useful in the preparation of salts useful as intermediates in obtaining compounds of the invention and their pharmaceutically acceptable acid addition salts.

Salts derived from appropriate bases include alkali metal (e.g. sodium), alkaline earth metal (e.g. magnesium), ammonium and NR_4^+ (where R is C_{1-4}alkyl) salts.

The compounds of formula (I) act as agonists at atypical beta - adrenoceptors and as such are useful in the treatment of clinical conditions susceptible to amelioration by administration of an atypical beta-adrenoceptor agonist. Such conditions include hyperglycaemia, obesity, hyperlipemia, irritable bowel syndrome and its associated pain, motility dysfunction, excessive gastrointestinal secretion, non-specific diarrhoea, neurogenic inflammation, depression, regulation of intraocular pressure, triglyceridemia, diabetes, e.g. non-insulin-dependent diabetes mellitus (NIDDM or Type II), such as obese NIDDM and non-obese NIDDM, diabetic complications such as retinopathy, nephropathy, neuropathy, cataracts, coronary heart diseases and arteriosclerosis, osteoporosis; and gastrointestinal disorders, particularly inflammatory gastrointestinal disorders.

We have found that the compounds of formula (I) are particularly useful for the treatment of gastrointestinal disorders, especially inflammatory gastrointestinal disorders such as peptic ulceration, oesophagitis, gastritis and duodenitis (including that induced by H.pylori), intestinal ulcerations (including inflammatory bowel disease, especially, ulcerative colitis, Crohn's disease and proctitis) and gastrointestinal ulcerations, especially when induced by drugs such as non-steroidal anti-inflammatory drugs (NSAIDs) or corticosteroids.

Accordingly the present invention provides a method of treatment of a mammal, including man, suffering from condition susceptible of amelioration by an atypical beta-adrenoceptor agonist which method comprises administering to the subject an effective amount of a compound of general formula (I) or a physiologically acceptable derivative thereof.

In a preferred aspect of the present invention, there is provided a method of treatment of a mammal, including man, suffering from a gastrointestinal disorder, especially inflammatory gastrointestinal disorders such as peptic ulceration, oesophagitis, gastritis, duodenitis, intestinal ulcerations and

gastrointestinal ulcerations, which method comprises administering to the subject an effective amount of a compound of general formula (I) or a physiologically acceptable derivative thereof.

In a particularly preferred aspect of the present invention, there is provided a method of treatment of a mammal, including man, suffering from a condition of gastrointestinal ulcerations wherein said condition is induced by non-steroidal anti-inflammatory drugs, which method comprises administering to the subject an effective amount of a compound of general formula (I) or a physiologically acceptable derivative thereof.

References in this specification to treatment include prophylactic treatment as well as the alleviation of symptoms.

In a further aspect, the present invention provides a compound of formula (I) or a physiologically acceptable derivative thereof for use as a therapeutic agent for use in medicine, particularly human medicine, in particular for the treatment of gastrointestinal disorders, in particular gatrointestinal disorders associated with inflammation or ulceration.

In a further aspect, the invention provides the use of a compound of general formula (I) or a physiologically derivative thereof, for the manufacture of a medicament for the treatment of a condition susceptible of amelioration by an atypical beta-adrenoceptor agonist.

In a further preferred aspect of the present invention, there is provided the use of a compound of general formula (I) or a physiologically acceptable salt or solvate thereof for the manufacture of a medicament for the treatment of gastrointestinal disorders.

It will be appreciated that where a compound of general formula (I) or a physiologically acceptable salt or solvate thereof is used for the treatment of a condition of gastrointestinal ulcerations induced by non-steroidal anti-

inflammatory drugs (NSAID's) it may be preferable to co-adminster the compound of general formula (I) together with the NSAID. The active ingredients may be employed in the form of separate pharmaceutical formulations or a combined formulation may be used. In such a combined formulation, the active ingredients must be stable and mutually compatible in the particular formulation employed.

While it is possible that, for use in therapy, a compound of the invention may be administered as the raw chemical it is preferable to present the active ingredient as a pharmaceutical formulation.

The invention thus further provides a pharmaceutical composition comprising a compound of formula (I) or a physiologically acceptable derivative thereof together with one or more pharmaceutically acceptable carriers therefor and, optionally, other therapeutic and/or prophylactic ingredients.

In particular, there are provided pharmaceutical compositions which comprise a compound of formula (I) and a non-steroidal anti-inflammatory drug, together with one or more pharmaceutically acceptable carriers. The compound of general formula (I) and their physiologically acceptable derivatives may be formulated for administration in any convenient way. The carrier(s) or excipient(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

Thus the compounds for use according to the present invention may be formulated for oral, buccal, parenteral, rectal or transdermal administration or in a form suitable for administration by inhalation or insufflation (either through the mouth or the nose).

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with

pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium starch glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with physiologically acceptable additives such as suspending agents (e.g. sorbitol syrup, cellulose derivatives or hydrogenated edible fats); emulsifying agents (e.g. lecithin or acacia); non-aqueous vehicles (e.g. almond oil, oily esters, ethyl alcohol or fractionated vegetable oils); and preservatives (e.g. methyl or propyl-p-hydroxybenzoates or sorbic acid). The preparations may also contain buffer salts, flavouring, colouring and sweetening agents as appropriate.

Preparations for oral administration may be suitably formulated to give controlled release of the active compound.

For buccal administration the compositions may take the form of tablets or lozenges formulated in conventional manner.

For transdermal administration the compounds according to the invention may be formulated as creams, gels, ointments or lotions or as a transdermal patch. Such compositions may for example be formulated with an aqueous or oily base with the addition of suitable thickening, gelling, emulsifying, stabilising, dispersing, suspending, and/or colouring agents.

The compounds according to the present invention may be formulated for parenteral administration by injection e.g. by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form

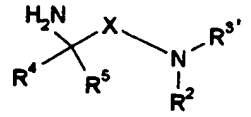
e.g. in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

The compounds according to the present invention may also be formulated in rectal compositions such as suppositories or retention enemas, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

In addition to the formulations described previously, the compounds may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example subcutaneously, transcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds according to the present invention may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

A proposed dose of the compounds according to the present invention for administration to a human (of approximately 70kg body weight) is 0.1mg to 1g, preferably to 1mg to 100mg of the active ingredient per unit dose, expressed as the weight of free base. The unit dose may be administered, for example, 1 to 4 times per day. The dose will depend on the route of administration. It will be appreciated that it may be necessary to make routine variations to the dosage depending on the age and weight of the patient as well as the severity of the condition to be treated. The precise dose and route of administration will ultimately be at the discretion of the attendant physician or veterinarian.

The compounds of the invention may be prepared by any of the processes known in the art for the preparation of similar compounds. For example, according to a first process (A), compounds of formula (I) may be prepared by reaction of a compound of formula (III) with a compound of formula (IV):



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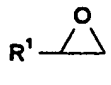
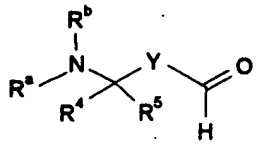


(IV)

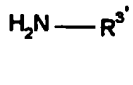
wherein R^1, R^2, R^3, R^4, R^5 and X are as defined for formula (I) and $R^{3'}$ represents the group R^3 wherein the carboxylic acid moiety/moieties is/are protected, for example as an alkyl ester or esters, followed by removal of the protecting group or groups.

The reaction is conveniently effected in a suitable organic solvent, such as dimethyl sulphoxide, acetonitrile or an alcohol such as 2-propanol, suitably at elevated temperature, such as about 60 to 100°C, optionally in the presence of N-trimethylsilylacetamide.

Compounds of formula (III) wherein R^2 is H may be prepared by reaction of an aldehyde of formula (V) with an amine of formula (VI)



(V)

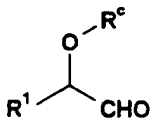


(VI)

wherein $R^{3'}$ is as defined for formula (III), Y represents a bond or CH_2, R^a represents a protecting group, and R^b represents a protecting group or H, in the presence of a reducing agent, followed by removal of the protecting group or groups.

Compounds of formula (III) wherein R^2 is C_{1-6}alkyl may be prepared from the corresponding compounds of formula (III) wherein R^2 is H by conventional alkylation procedures.

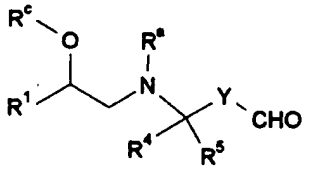
According to a second process (B), compounds of formula (I) may also be prepared by reaction of a compound of formula (III) as defined above with a compound of formula (VII)



(VII)

wherein R^1 is as defined for formula (I) and R^c is a protecting group, in the presence of a reducing agent, followed by removal of the protecting groups.

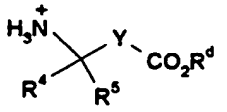
According to a third process (C), compounds of formula (I) where R^2 is H may also be prepared by reaction of an amine of formula (VI) as defined above, with a compound of formula (VIII)



(VIII)

wherein R^1, R^4, R^5 and R^a, R^c, and Y are as defined as for formulae (I), (V) and (VII), in the presence of a reducing agent, followed by removal of the protecting groups.

Compounds of formula (VIII) may be prepared by reaction of compounds of formula (VII), as defined as above, with an amine acid salt of formula (IX)



(IX)

wherein R^4, R^5 and Y are as defined herein before, and R^d is a suitable alkyl group for protection, in the presence of a reducing agent. Following protection of the nitrogen, the ester is reduced by a suitable reducing agent such as Di-isobutyl aluminium hydride.

Suitable reducing agents of use in the reductions include hydrogen in the presence of a catalyst, such as a noble metal catalyst, for example palladium, platinum or platinum oxide, Raney-nickel or hydride reducing agents such as borohydrides, for example sodium borohydride, sodium triacetoxyborohydride, or sodium cyanoborohydride. Suitable reaction conditions will be readily apparent to those skilled in the art and are further illustrated by the accompanying examples.

Compounds of formula (IV), (V), (VI), (VII) and (IX) are known compounds or may be prepared from the known compounds by standard procedures well known to those skilled in the art.

The protecting groups used in the preparation of compounds of formula (I) may be used in conventional manner. See for example 'Protective Groups in Organic Chemistry' Ed. J. F. W. McOmie (Plenum Press 1973) or 'Protective Groups in Organic Synthesis' by Theodora W Greene and P M G Wuts (John Wiley and Sons 1991).

Conventional amino protecting groups may include for example aralkyl groups, such as benzyl, diphenylmethyl or triphenylmethyl groups; and acyl groups such as N-benzyloxycarbonyl or t-butoxycarbonyl.

Conventional oxygen protecting groups may include for example alky silyl groups, such as trimethyl silyl, or tert-butyldimethyl silyl; alkylethers such as tetrahydropyranyl, or tert-butyl; or esters such as acetate.

Removal of any protecting groups present may be achieved by conventional procedures.

Atypical beta-adrenoceptor agonists are compounds which demonstrate a pharmacological response mediated at atypical beta-adrenoceptors. This activity has been be measured as the ability to stimulate lipolysis by rat adipocytes at sub-micromolar concentrations, in a response that is resistant to blockade by standard beta-adrenoceptor blocking drugs such as propranolol.

Another useful means of identifying an atypical beta-adrenoceptor agonist involves the measurement of agonist activity at atypical beta-adrenoceptors in the rat isolated lower oesophagus. A suitable assay is described below as Method 1. Typically in this assay, a compound of general formula (I) for use according to the present invention has an equipment molar ratio (EPMR) relevant to isoprenaline of less than 30.

The rat oesophagus assay is based upon that described by Ford *et. al.*, *Br. J. Pharmacol.*, 105(suppl.), 235P, 1992, the method of which is described below as Method 1:

Method 1

The lower oesophagus is removed from male AH/A rats (100-150g). The overlying serosal muscle is removed from the oesophagus to leave the tunis muscularis mucosa. Tissues are then placed in Kreb's solution containing the $ß_2$-antagonist ICI 118,551 (10^{-6}M), the $ß_1$-antagonist atenolol (10^{-5}M), the phosphodiesterase inhibitor isobutyl methyl xanthine (IBMX; $3x10^{-6}$M) and the prostaglandin synthesis inhibitor indomethacin ($3x10^{-6}$M), and the tissues suspended under a resting tension of 0.5g.

Subsequently, tissues are contracted with a submaximal concentration of carbachol (10^{-6}M) and, when a stable increase in tension has been achieved, a cumulative concentration effect curve to isoprenaline is constructed. Following washout with fresh Kreb's solution, tissues are recontracted with carbachol (10^{-6}M) and a cumulative concentration effect curve to test agonist is constructed.

The relative potency of each test agonist (EPMR) is compared to isoprenaline as follows:

$$EPMR = \frac{EC_{50} \text{ agonist}}{EC_{50} \text{ isoprenaline}}$$

wherein EC_{50} is the molar concentration of agonist which produces 50% of the maximum possible response for that agonist.

Using the non-selective beta-adrenoceptor agonist isoprenaline as a reference agonist, compounds selective for atypical beta-adrenoceptors should preferably be a minimum of 10-30 times less potent than isoprenaline at $ß_1$- or $ß_2$-adrenoceptors and, more preferably, 300-1000 times less potent than isoprenaline at $ß_1$- or $ß_2$-adrenoceptors.

A particularly useful method for determining agoinst activity at human atypical beta-adrenoceptors involves the use of Chinese hamster ovarian (CHO) cells transfected with the human beta-3-adrenoceptor according to Method 2.

Method 2

Cell culture

General cell culture guidelines are observed (Fershney, R.A. (1987) Culture of animal cells: A manual of basic technique. Wiley-Liss, Inc., N.Y.). A standard cell culture incubator is used (37°C, 5% CO_2 in air, 95%

relative humidity). H β_3CHO cells are grown in 75ml flasks in MEMα medium containing 9% FCS & 125μg/ml G418. One confluent flask of cells is trypsinised and resuspended in 80ml of culture medium; 1ml of the cell suspension is added to each well of three 24-well plates. The plates are then incubated for 1 day.

Experimental method

The medium is aspirated from each well, and the well rinsed with phosphate-buffered saline (PBS, this is then aspirated). 1ml of MEMα (no FCS or G418, 300μM IBMX) is added to each well. Antagonists, if required, are added at this stage. The plate is then placed back in the incubator for 30min. Drugs are then added to the wells (10μl, 100x required final concentration), the plate gently swirled to mix the drugs, and the plate placed back in the incubator for 30 min. The medium is then aspirated from each well, the well rinsed with PBS, and 0.5ml perchloric acid (6% v/v in distilled water, 2-5°C). The plate is left on ice for 30min. The perchloric acid (containing cAMP) is transferred to a clean 24-well plate and the acid neutralised by addition of saturated $KHCO_3$ solution (200μl) to each well. The plate is then swirled and frozen (-20°C) until cAMP is assayed. cAMP is assayed using an enzyme-immunoassay kit (Amersham).

The relative protency of the test compounds are compared to isoprenaline as described in Method 1.

An experimental model in which atypical beta-adrenoceptor agonists may be shown to be of use in the treatment of gastrointestinal disorders is described below as Method 3. The procedure is based upon that described by H. Satoh et. al., *Gastroenterology*, 81, 719-725 (1981) in which the effect of compounds on indomethacin-induced gastric antral lesions in the re-fed rat is investigated. Indomethacin is an example of the class of compound known as non-steroidal anti-inflammatory drugs (NSAIDs), the use of which is frequently associated with gastrointestinal ulcers.

Method 3

Food (but not water) is withheld from female random hooded rats (70-120g) for 24 hours and then the rats are re-fed with Rat and Mouse No. 1 Maintenance Diet. After 1 hour of access to food, the rats are dosed orally with either the test compound or solvent (0.5% w/v methyl cellulose in water). 30 minutes later, indomethacin (60mg/kg; dissolved in 1% w/v $NaHCO_3$ in saline) is administered as a single subcutaneous injection at the back of the neck. Subsequently, the rats are allowed food, but water is withheld, and the animals are humanely killed by cervical dislocation at 6 hours post dose. Control animals received a single subcutaneous dose of the appropriate solvent.

The rat's stomach is removed (with a small amount of duodenum attached), opened along the greater curvature and the contents removed by washing with 0.9% w/v sodium chloride solution (saline). The opened stomach is pinned out (mucosal surface uppermost) on a polystyrene mat and the area of damage assessed by placing a grid (composed of 1mm squares) over the antral region. Antral damage appears as discrete black or dark brown ulcers. The total area of antral damage is then expressed as a percentage of the total surface area of the antrum.

The protective effect of the test compound on indomethacin-induced antral damage is calculated as a percentage using the following equation:

$$100 \times \frac{\text{\% area of damage with NSAID} - \text{\% area of damage with NSAID + test compound}}{\text{\% area of damage with NSAID}}$$

The invention is further illustrated by the following intermediates and examples. All temperatures are in degrees centigrade. Flash

chromatography was carried out on silica (Merck 9385). Organic extracts were dried, where indicated, over anhydrous sodium sulphate.

Intermediate 1

(R)-(3-chloro-phenyl)-hydroxy-acetic acid methyl ester

A solution of (R)-(3-chloro-phenyl)-hydroxy-acetic acid (19.98g) in methanol (250ml) containing concentrated sulphuric acid (1ml) was heated under reflux for 6.5h. The solution was cooled, neutralised with aqueous sodium bicarbonate solution, and concentrated. The residue, dissolved in ethyl acetate, was washed with aqueous sodium bicarbonate solution, dried, and evaporated to give the title compound (21.13g) as a pale-yellow oil

$[\alpha]_D$ -104° (c 1.00 MeOH)

Intermediate 2

(R)-(tert-butyl-dimethyl-silanoxy)-(3-chloro-phenyl)-acetic acid methyl ester

A solution of (R)-(3-chloro-phenyl)-hydroxy-acetic acid methyl ester (21.0g), imidazole (14.25g), and tert-butyldimethylsilyl chloride (25.0g) in N,N-dimethylformamide (250ml) was stirred at room temperature for 18h. The mixture was poured into water (2.5l) and extracted with ethyl acetate (3x500ml). The combined extracts were washed with water and saturated brine, dried, and concentrated. The residue was purified by chromatography on silica, eluting with cyclohexane:ethyl acetate (9:1) to give the title compound as a colourless oil (32.625g)

$[\alpha]_D$ -55.4° (c 1.21 MeOH)

Intermediate 3

(R)-(tert-butyl-dimethyl-silanoxy)-(3-chloro-phenyl)-acetaldehyde

To a stirred solution of (R)-(tert-butyl-dimethyl-silanoxy)-(3-chloro-phenyl)-acetic acid methyl ester (4.0g) in anhydrous ether (10ml) and maintained at <-65° was added dropwise a 1.5M solution of di-isobututylaluminium hydride in toluene (10ml). When addition was complete the solution was stirred at -65° for a further hour, then quenched with methanol (10ml). The

mixture was allowed to attain room temperature when silica (20g) was added. Solvent was removed under reduced pressure, and the solid was chromatographed on silica, eluting with cyclohexane:ethyl acetate (9:1). Evaporation of the appropriate fractions gave the title compound as a colourless liquid (3.09g)

$[\alpha]_D$ -45.3^o (c 1.50 MeOH)

Intermediate 4

(5-Nitropyridin-2-yl) acetic acid ethyl ester

To a stirred mixture of 2-chloro-5-nitropyridine (3.0g) and sodium hydride (60% dispersion in oil, 1.51g) in N,N-dimethylformamide (30ml) was added slowly tert-butyl ethyl malonate (7.17ml), then the mixture was stirred at room temperature for 4h. The reaction mixture was poured into water (300ml), and extracted with ethyl acetate. The combined extracts were washed with water, dried, and concentrated. The residue was chromatographed on silica, eluting with cyclohexane:ethyl acetate (4:1). Concentration of the relevant fractions gave tert-butyl ethyl 2-(5-nitro-pyridin-2-yl)-malonate as a yellow oil (3.43g)

A solution of this ester (2.16g) in dichloromethane (20ml) was treated with trifluoroacetic acid (1.61ml) for 0.5h. The solution was washed with aqueous sodium bicarbonate solution, dried and evaporated to give the title compound as an orange oil (1.42g)

Assay: Found: C 51.4; H 4.8; N 13.3%

$C_9H_{10}N_2O_4$ requires C 51.5; H 5.0; N 13.1%

Intermediate 5

(5-amino-pyridin-2-yl)-acetic acid, ethyl ester

A mixture of (5-nitropyridin-2-yl) acetic acid ethyl ester (1.405g), ammonium formate (2.11g), 10% palladium on charcoal (0.20g), and ethanol (30ml) was heated under reflux for 1.5h. The mixture was filtered, and the filtrate, after concentration, was chromatographed on silica, eluting with

chloroform:methanol (19:1). Concentration of the relevant fractions gave the title compound as a yellow oil (1.105g)

Assay: Found: C 57.9; H 6.6; N 15.0%

$C_9H_{12}N_2O_2.0.33H_2O$ requires C 58.05; H 6.9; N 15.0%

Intermediate 6

4-Nitrobenzo[1,3]dioxole-2-carboxylic acid ethyl ester

A mixture of 4-nitrocatechol (10.18g), ethyl dichloroacetate (8.86ml), and potassium carbonate (13.59g) in N,N-dimethylformamide (100ml) was stirred at room temperature for 2 weeks. The mixture was partitioned between 2N hydrochloric acid and ethyl acetate, the phases were separated, and the aqueous phase was extracted further with ethyl acetate. The combined organic extracts were dried and evaporated. Chromatography of the residue on silica eluting with cyclohexane:ethyl acetate (4:1), and concentration of the relevant fractions gave the title compound as pale yellow crystals (1.39g).

$C_{10}H_9NO_6$: MH^+ 240.0506 (to 0.7 ppm)

Intermediate 7

4-Aminobenzo[1,3]dioxole-2-carboxylic acid ethyl ester

4-Nitrobenzo[1,3]dioxole-2-carboxylic acid ethyl ester (1.38g) in ethanol (20ml) was treated with platinum dioxide (0.13g) in an atmosphere of hydrogen for 18h. The mixture was filtered under an atmosphere of nitrogen, and the filtrate was concentrated to give the title compound as a yellow oil (0.895g)

$C_{10}H_{11}NO_4$: MH^+ 210

Intermediate 8

{4-[2R-(tert-Butoxycarbonylamino)-propylamino]-phenyl-}acetic acid ethyl ester

A solution of (1R-methyl-2-oxo-ethyl)-carbamic acid tert-butyl ester (1.163g) in dry dichloromethane (50ml) was sequentially treated with 4-amino-phenylacetic acid ethyl ester (1.734g), acetic acid (0.84ml), and sodium

triacetoxyborohydride (3.88g). The mixture was stirred under an atmosphere of nitrogen for 48h, then washed with water, sodium bicarbonate solution, and saturated brine. The organic phase was dried and concentrated under reduced pressure, and the residue was chromatographed on silica, eluting with cyclohexane:ethyl acetate (3:1). Concentration of the appropriate fractions gave the title compound as a colourless gum (1.282g).

Assay: Found: C 63.5; H 8.1; N 8.3%

$C_{18}H_{28}N_2O_4.0.25H_2O$ requires C 63.4; H 8.4; N 8.2%

Similarly prepared were:

Intermediate 9

[4-[2-(tert-Butoxycarbonylamino)-2-methypropylamino]phenyl] acetic acid, methyl ester as a brown crystalline solid (0.75g)

Assay: Found C 64.2; H 8.2; N 8.2%

$C_{18}H_{27}N_2O_4$ requires C 64.4; H 8.3; N 8.3%

from (1,1-dimethyl-2-oxo-ethyl)-carbamic acid tert-butyl ester (0.50g) and 4-aminophenylacetic acid methyl ester (0.441g)

Intermediate 10

{4-[2R-(N,N-dibenzylamino)-propylamino]-phenyl-}acetic acid ethyl ester as a yellow oil (13.45g)

$C_{27}H_{32}N_2O_2$: MH^+ 417

from 2R-dibenzylamino-propionaldehyde (10.37g) and 4-aminophenylacetic acid ethyl ester (6.77g);

Intermediate 11

{3-[2R-(N,N-dibenzylamino)-propylamino]-phenyl}-acetic acid methyl ester as a colourless oil (0.483g)

$[\alpha]_D$ +91.1 (c 1.23, CH_2Cl_2]

from 2R-dibenzylamino-propionaldehyde (0.771g) and 4-aminophenylacetic acid methyl ester (0.503g);

Intermediate 12

[4-[2-(tert-Butoxycarbonylamino)-ethylamino]-phenyl]-acetic acid, methyl ester as a pale yellow oil (0.18g)

$C_{17}H_{26}N_2O_4$: MH^+ 323

from (1R-methyl-2-oxo-ethyl)-carbamic acid tert-butyl ester (0.22g) and 4-aminophenylacetic acid methyl ester (0.24g)

Intermediate 13

{4-[(1-tert-Butoxycarbonylamino-cyclopropylmethyl)-amino]phenyl}-acetic acid ethyl ester as an off-white crystalline solid (0.472g)

n.m.r. ($CDCl_3$): δ 0.87 (dd, 4H), 1.20 (t, 3H), 1.41 (s, 9H), 3.18 (s, 2H), 3.47 (s, 2H), 4.13 (q, 2H), 5.00 (broad s, 1H), 6.51 (d, 2H), 7.04 (d, 2H)

from (1-formyl-cyclopropyl)-carbamic acid tert-butyl ester (0.30g) and 4-aminophenylacetic acid ethyl ester (0.29g)

Intermediate 14

[4-[2R-2-(tert-Butoxycarbonylamino)-3-methyl-butylamino]phenyl]acetic acid, methyl ester as a yellow oil (0.986g)

$C_{19}H_{30}N_2O_4$: MH^+ 351

from (1R-formyl-2-methyl-propyl)-carbamic acid tert-butyl ester (0.80g) and 4-aminophenylacetic acid methyl ester (0.657g)

Intermediate 15

{4-[(2-(tert-Butoxycarbonylamino-propyl)-methyl-amino]phenyl}-acetic acid ethyl ester as a pale yellow oil (0.84g), as a 3:1 mixture of (R) and (S) isomers

$C_{19}H_{30}N_2O_4$: MH^+ 351

from (1R-methyl-2-oxo-ethyl)-carbamic acid tert-butyl ester (0.59g) and 4-(methylamino)-phenylacetic acid ethyl ester (0.66g)

Intermediate 16

[4-[2-(tert-Butoxycarbonylamino)-ethyl)-methyl-amino]phenyl]acetic acid, ethyl ester as a yellow gum (0.843g)

n.m.r. ($CDCl_3$): δ 1.25 (t, 3H), 1.45 (s, 9H), 2.95 (s, 3H), 3.25-3.50 (m, 4H), 3.52 (s, 2H), 4.13 (q, 2H), 4.72, (m, 1H), 6.72-7.15 (dd, 4H).

from (2-oxo-ethyl)-carbamic acid tert-butyl ester (1.8g) and 4-(methylamino)-phenylacetic acid ethyl ester (0.75g)

Intermediate 17

{5-[(1-tert-Butoxycarbonylamino-cyclopropylmethyl)-amino]-pyridin-2-yl}-acetic acid, methyl ester as fawn crystals (0.285g)

n.m.r. ($CDCl_3$): δ 0.86 (dd, 4H), 1.43 (s, 9H), 3.18 (d, 2H), 3.69 (s, 3H), 3.71 (s, 2H), 5.01 (broad s, 1H), 6.83 (dd, 1H), 7.05 (d, 1H), 7.93 (d, 1H)

from (1-formyl-cyclopropyl)-carbamic acid ter-butyl ester (0.30g) and 5-aminopyridin-2-yl-acetic acid methyl ester (0.269g)

Intermediate 18

[5-(2R-tert-Butoxycarbonylamino-propylamino)-pyridin-2-yl]-acetic acid, ethyl ester as a yellow oil (0.905g)

$C_{17}H_{27}N_3O_4$: MH^+ 338

from (1R-methyl-2-oxo-ethyl)-carbamic acid tert-butyl ester (0.634g) and 5-aminopyridin-2-yl-acetic acid ethyl ester (0.60g)

Intermediate 19

2-[2R-(tert-Butoxycarbonylamino)-propylamino]-thiazol-4-yl-acetic acid, ethyl ester as a brown gum (0.507g

$C_{15}H_{25}N_3O_4S$: MH^+ 343

from (1R-methyl-2-oxo-ethyl)-carbamic acid tert-butyl ester (0.688g) and 2-aminothiazol-4-yl-acetic acid ethyl ester (0.973g)

Intermediate 20

4-[2R-(tert-Butoxycarbonylamino)-propylamino]-benzo[1,3]dioxole-2-carboxylic acid, ethyl ester as a colourless oil.(1.289g)

$C_{18}H_{26}N_2O_6$: MH^+ 367

from (1R-methyl-2-oxo-ethyl)-carbamic acid tert-butyl ester (0.729g) and 4-aminobenzo[1,3]dioxole-2-carboxylic acid ethyl ester (0.88g)

Intermediate 21

[4-(2R-Amino-propylamino)-phenyl]-acetic acid ethyl ester

A stirred mixture of {4-[2R-(N,N-dibenzylamino)-propylamino]-phenyl-}acetic acid ethyl ester (6.70g), ammonium formate (13.98g), 10% palladium on charcoal (1.2g), and methanol (190ml) was heated under reflux for 2h. The mixture was cooled and filtered, and the filtrate was concentrated. The residue was chromatographed on silica, eluting with chloroform:methanol:0.880 ammonia solution (60:10:1). Concentration of the appropriate fractions gave the title compound as a pale yellow oil (3.23g)

$C_{13}H_{20}N_2O_2$: MH^+ 237

Similarly prepared was:

Intermediate 22

[3-(2R-Amino-propylamino)-phenyl]-acetic acid methyl ester as a pale yellow oil (0.18g)

$C_{12}H_{18}N_2O_2$: MH^+ 223

from {3-[2R-(N,N-dibenzylamino)-propylamino]-phenyl}-acetic acid methyl ester (0.45g);

Intermediate 23

(4-{2R-[2-(3-Chlorophenyl)-2R-hydroxy-ethylamino]propylamino}-phenyl)-acetic acid methyl ester

A solution of [4-(2R-Amino-propylamino)-phenyl]-acetic acid ethyl ester (0.367g) in dimethyl sulphoxide (1.5ml) was treated with N-

trimethylsilylacetamide (0.434g), and the solution was stirred under an atmosphere of nitrogen for 24h. A solution of (R)-3-chlorophenyloxirane (0.281g) in dimethylsulphoxide (1.5ml) was added and the mixture was heated at 65-75° for 48h. The mixture was poured into 2N hydrochloric acid (50ml) and ethyl acetate (50ml), and the resultant mixture was stirred vigorously for 1.5h. The phases were separated, and the aqueous phase was extracted with ethyl acetate. The combined organic extracts were washed with saturated brine, then dried and concentrated under reduced pressure. The residue was chromatographed on silica, eluting with 5% methanol in dichloromethane. Concentration of the appropriate fractions gave the title compound as a pale-brown foam (0.134g).

Assay Found: C 62.0; H 6.7; N 7.1%

$C_{20}H_{25}ClN_2O_3.0.5H_2O$ requires C 62.25; H 6.8; N 7.3%

Intermediate 24

[4-(2R-Amino-propylamino)-phenyl]-acetic acid methyl ester

A solution of {4-[2R-(tert-Butoxycarbonylamino)-propylamino]-phenyl}-acetic acid ethyl ester (0.7g) in methanol (40ml) was treated with 9M hydrogen chloride in methanol (4ml), and the solution was stirred for 48h. The solution was concentrated to a quarter of its volume and diluted with ethyl acetate (50ml) and this mixture was washed with sodium carbonate solution. The organic phase was separated, washed with saturated brine, and dried. Evaporation of the solvent gave the title compound as a colourless gum (0.394g).

Assay Found: C 63.3; H 8.0; N 11.8%

$C_{12}H_{18}N_2O_2.0.4MeOH$ requires C 63.35; H 8.4; N 11.9%

Similarly prepared were:

Intermediate 25

[4-[2-amino)-2-methypropylamino]-phenyl]-acetic acid, methyl ester as a fawn oil (0.823g)

n.m.r. ($CDCl_3$): δ 1.20 (s, 6H), 2.95 (broad s, 2H), 3.50 (s, 2H), 3.68 (s, 3H), 4.12 (broad s, 1H), 6.62 (d, 2h), 7.08 (d, 2H).

from [4-[2-(tert-Butoxycarbonylamino)-2-methypropylamino]-phenyl]-acetic acid, methyl ester (1.374g);

Intermediate 26

[4-(2-Amino-ethylamino)-phenyl]-acetic acid, ethyl ester as a pale brown oil (0.09g)

$C_{12}H_{18}N_2O_2$: MH^+ 223.144257 (to 1.8 ppm)

from [4-[2-(tert-Butoxycarbonylamino)-ethylamino]-phenyl]-acetic acid, methyl ester (0.16g), using hydrogen chloride in ethanol;

Intermediate 27

[4-(1-Amino-cyclopropylmethyl)amino]-phenylacetic acid, methyl ester as a yellow oil (0.28g)

n.m.r. ($CDCl_3$): δ 0.52-0.70 (m, 4H), 1.53 (broad s, 2H), 3.08 (s, 2H), 3.51 (s, 2H), 3.68 (s, 3H), 6.63 (d, 2H), 7.09 (d, 2H)

from {4-[(1-tert-Butoxycarbonylamino-cyclopropylmethyl)-amino]-phenyl}-acetic acid, ethyl ester (0.436g);

Intermediate 28

[4-(2R-Amino-3-methylbutyl)amino]-phenylacetic acid, methyl ester as a brown oil (0.578g)

$C_{14}H_{22}N_2O_2$: MH^+ 251

from [4-[2R-2-(tert-Butoxycarbonylamino)-3-methyl-butylamino]-phenyl]-acetic acid, methyl ester (0.83g);

Intermediate 29

[4-(2-Amino-propyl)-methyl-amino]phenylacetic acid, ethyl ester as a pale brown oil (0.12g)

$C_{14}H_{22}N_2O_2$: MH^+ 251.1761 (to 0.6 ppm)

from {4-[(2-(tert-Butoxycarbonylamino-propyl)-methyl-amino]-phenyl}-acetic acid, ethyl ester (0.34g), using hydrogen chloride in ethanol;

Intermediate 30

[4-(2-Amino-ethyl)-methyl-amino]-phenylacetic acid, methyl ester hydrochloride as a colourless foam (0.66g) from [4-[2-(tert-Butoxycarbonylamino)-ethyl)-methyl-amino]phenyl]acetic acid, ethyl ester (0.757g) without the neutralisation step, (used immediately to prepare (4-{2-[2-(tert-Butyl-dimethyl-silanyloxy)-2-(3-chloro-phenyl)-ethylamino]-ethyl)-methyl-amino}-phenyl)-acetic acid methyl ester)

Intermediate 31

{5-[(1-Aminocyclopropylmethyl)-amino]-pyridin-2-yl}-acetic acid, methyl ester as a yellow oil (0.158g)

n.m.r. ($CDCl_3$): δ 0.54-0.72 (m, 4H), 1.60 (broad s, 2H), 3.09 (d, 2H), 3.70 (s, 3H), 3.73 (s, 2H), 6.90 (dd, 1H), 7.09 (d, 1H), 8.06 (d, 1H)

from {5-[(1-tert-Butoxycarbonylamino-cyclopropylmethyl)-amino]-pyridin-2-yl}-acetic acid, methyl ester (0.246g);

Intermediate 32

[5-(2R-Amino-propyl)amino]-pyridin-2-ylacetic acid, ethyl ester hydrochloride as a yellow solid (0.305g)

Assay: Found: C 61.5; H 7.9; N 8.0%

$C_{12}H_{21}N_3O_2$ .HCl requires C 61.7; H 7.9; N 8.3%

from [5-(2R-tert-Butoxycarbonylamino-propylamino)-pyridin-2-yl]-acetic acid, ethyl ester (0.333g) using hydrogen chloride in ethanol,without the neutralisation step;

Intermediate 33

2-[(2R-Amino-propyl)amino]-thiazole-4-acetic acid, ethyl ester hydrochloride as a yellow solid (0.135g) from 2-[2R-(tert-Butoxycarbonylamino)-propylamino]-thiazol-4-yl-acetic acid, ethyl ester

(0.14g), using hydrogen chloride in ethanol, without the neutralisation step; (used immediately to prepare (2-{2R-[2R-(tert-Butyl-dimethyl-silanyloxy)-2-(3-chloro-phenyl)-ethylamino]-propylamino}-thiazol-4-yl)-acetic acid ethyl ester)

Intermediate 34

4-[(2R-Aminopropyl)-amino]-benzodioxole-2-carboxylic acid, methyl ester hydrochloride as a yellow foam (0.462g)

n.m.r. (DMSO-d_6): δ 1.21 (d, 3H), 3.0-3.55 (m, 3H), 3.76 (s, 3H), 6.12-6.88 (m, 4H), 7.91-8.36 (m, 4H).

from 4-[2R-(tert-Butoxycarbonylamino)-propylamino]-benzo[1,3]dioxole-2-carboxylic acid, ethyl ester (0.533g), without the neutralisation step.

Intermediate 35

(4-{2R-[2R-(tert-Butyl-dimethyl-silanyloxy)-2-(3-chloro-phenyl)-ethylamino]-propylamino}-phenyl)-acetic acid ethyl ester

A solution of [4-(2R-Amino-propylamino)-phenyl]-acetic acid ethyl ester (3.2g) and (R)-(tert-butyl-dimethyl-silanoxy)-(3-chloro-phenyl)-acetaldehyde (3.93g) in dichloromethane (120ml) containing acetic acid (0.75ml) was stirred at 5° for 0.25h, then sodium triacetoxyborohydride (5.74g) was added, and the mixture was stirred for 3.5h. The resultant solution was washed with aqueous sodium bicarbonate solution, dried and concentrated. The residue was chromatographed on silica; elution with cyclohexane:ethyl acetate (1:2) and concentration of the relevant fractions gave the title compound as a pale yellow oil (5.76g).

n.m.r. ($CDCl_3$): δ values include -0.15 (s, 3H), 0.03 (s, 3H), 0.86 (s, 9H), 1.17 (d, 2H), 3.48 (s, 2H), 4.13 (q, 2H), 4.80 (m, 1H), 6.54 (d, 2H), 7.08 (d, 2H).

Similarly prepared were:

Intermediate 36

(3-{2R-[2R-(tert-Butyl-dimethyl-silanyloxy)-2-(3-chloro-phenyl)-ethylamino]-propylamino}-phenyl)-acetic acid ethyl ester as a pale yellow oil (0.25g)

$C_{26}H_{39}ClN_2O_3Si$: MH^+ 491.251072 (error to 2.8 ppm)

from [3-(2R-Amino-propylamino)-phenyl]-acetic acid methyl ester (0.18g) and (R)- (tert-butyl-dimethyl-silanoxy)-(3-chloro-phenyl)- acetaldehyde (0.23g);

Intermediate 37

(4-{2-[2R-(tert-Butyl-dimethyl-silanyloxy)-2-(3-chloro-phenyl)-ethylamino]-methylpropylamino}-phenyl)-acetic acid ethyl ester as a colourless oil (1.126g)

Assay: Found: C 64.3; H 8.3; N 5.6%

$C_{27}H_{41}ClN_2O_3Si$ requires C 64.2; H 8.1; N 5.55%

from {4-[2R-(tert-Butoxycarbonylamino)-propylamino]-phenyl-}acetic acid ethyl ester (0.823g) and (R)-(tert-butyl-dimethyl-silanoxy)-(3-chloro-phenyl)-acetaldehyde (0.992g);

Intermediate 38

(4-{2-[2R-(tert-Butyl-dimethyl-silanyloxy)-2-(3-chloro-phenyl)-ethylamino]-ethylamino}-phenyl)-acetic acid ethyl ester as a colourless oil (0.14g)

$C_{26}H_{39}ClN_2O_3Si$: MH^+ 491.247739 (error to 3.9 ppm)

from [4-(2-Amino-ethylamino)-phenyl]-acetic acid, ethyl ester (0.09g) and (R)-(tert-butyl-dimethyl-silanoxy)-(3-chloro-phenyl)-acetaldehyde (0.12g);

Intermediate 39

(4-{[1-(2R-(tert-Butyl-dimethyl-silanyloxy)-2-(3-chloro-phenyl)-ethylamino)-cyclopropylmethyl]-amino}-phenyl)-acetic acid methyl ester as a yellow oil (0.44g)

n.m.r. ($CDCl_3$): δ-0.14 (s, 3H), 0.02 (s, 3H), 0.49-0.65 (m, 4H), 0.88 (s, 9H), 2.76 (m, 2H), 2.98 (q, 2H), 3.52 (s, 2H), 3.68 (s, 3H), 4.63 (q, 1H), 6.53 (s 2H), 7.08 (d, 2H), 7.13-7.31 (m, 4H)

from [4-(1-Amino-cyclopropylmethyl)amino]-phenylacetic acid, methyl ester (0.272g) and (R)-(tert-butyl-dimethyl-silanoxy)-(3-chloro-phenyl)-acetaldehyde (0.331g);

Intermediate 40

(4-{2-[2R-(tert-Butyl-dimethyl-silanyloxy)-2-(3-chloro-phenyl)-ethylamino]-3-methyl-butylamino}-phenyl)-acetic acid methyl ester as a colourless oil (1.082g)

Assay: Found: C 64.8; H 8.2; N 5.4; Cl 6.9%

$C_{28}H_{43}ClN_2O_3Si$ requires C 64.8; H 8.3; N 5.4; Cl 6.85%

from [4-(2R-Amino-3-methylbutyl)amino]phenylacetic acid, methyl ester (0.557g) and (R)-(tert-butyl-dimethyl-silanoxy)-(3-chloro-phenyl)-acetaldehyde (0.634g);

Intermediate 41

(4-{2-[2R-(tert-Butyl-dimethyl-silanyloxy)-2-(3-chloro-phenyl)-ethylamino]-ethyl)-methyl-amino}-phenyl)-acetic acid methyl ester as a colourless oil (0.155g)

$[\alpha]_D$ -37.1° (c 1.05, CH_2Cl_2)

from [4-(2-Amino-ethyl)-methyl-amino]phenylacetic acid, methyl ester (0.415g) and (R)-(tert-butyl-dimethyl-silanoxy)-(3-chloro-phenyl)-acetaldehyde (0.40g);

Intermediate 42

(5-[1-{2-[2R-(tert-Butyl-dimethyl-silanyloxy)-2-(3-chloro-phenyl)]-ethylamino} cyclopropylmethyl]-amino-pyridin-2-yl)-acetic acid methyl ester as a yellow oil (0.277g)

n.m.r. ($CDCl_3$): δ -0.14 (s, 3H), 0.03 (s, 3H), 0.46-0.0.69 (m, 4H), 0.84 (s, 9H), 2.70 (m, 2H), 2.93 (q, 2H), 3.69 (s, 3H), 3.72 (s, 2H), 4.62 (q, 1H), 6.79 (dd, 1H), 7.04 (d, 1H), 7.10-7.31 (m, 4H), 7.90 (d, 1H)

from [5-(1-Aminocyclopropyl-1-methyl)amino]pyridy-2-acetic acid, methyl ester (0.152g) and (R)-(tert-butyl-dimethyl-silanoxy)-(3-chloro-phenyl)-acetaldehyde (0.184g);

Intermediate 43

(5-{2R-[2R-(tert-Butyl-dimethyl-silanyloxy)-2-(3-chloro-phenyl)-ethylamino]-propylamino}-pyridin-2-yl)-acetic acid ethyl ester as a colourless oil (0.113g)

Assay: Found: C 61.5; H 7.9; N 8.0%

$C_{26}H_{40}ClN_3O_3Si$ requires C 61.7; H 7.9; N 8.3%

from [5-(2R-Amino-propyl)amino]-pyridin-2-ylacetic acid, ethyl ester (0.221g) and (R)- (tert-butyl-dimethyl-silanoxy)-(3-chloro-phenyl)-acetaldehyde (0.214g);

Intermediate 44

(2-{2R-[2R-(tert-Butyl-dimethyl-silanyloxy)-2-(3-chloro-phenyl)-ethylamino]-propylamino}-thiazol-4-yl)-acetic acid ethyl ester as a colourless oil (0.059g)

$C_{24}H_{38}ClN_3O_3SSi$: MH^+ 592

from 2-[(2R-Amino-propyl)amino]-thiazole-4-acetic acid, ethyl ester (0.129g) and (R)- (tert-butyl-dimethyl-silanoxy)-(3-chloro-phenyl)-acetaldehyde (0.116g);

Intermediate 45

(5-{2R-[2R-(tert-Butyl-dimethyl-silanyloxy)-2-(3-chloro-phenyl)-ethylamino]-propylamino}-benzo[1,3]dioxol-2-yl)-acetic acid methyl ester as a pale yellow oil (0.431g)

$C_{26}H_{37}ClN_2O_5Si$: MH^+ 523

from 4-[(2R-Aminopropyl)-amino]-benzodioxole-2-carboxylic acid, methyl ester (0.458g) and (R)-(tert-butyl-dimethyl-silanoxy)-(3-chloro-phenyl)-acetaldehyde (0.399g);

Intermediate 46

2R-[2R-(tert-Butyl-dimethyl-silanyloxy)-2-(3-chloro-phenyl)-ethylamino]-propionic acid methyl ester

(R)-(tert-butyl-dimethyl-silanoxy)-(3-chloro-phenyl)-acetaldehyde (2.317g) was added to a stirred solution of (R)-2-aminopropionic acid methyl ester hydrochloride (1.135g) in dichloromethane (50ml). The solution was stirred for 15min, then sodium triactetoxyborohydride (3.448g) was added, and the mixture was stirred a further 18h. The solution was washed with aqueous sodium bicarbonate solution, then the organic phase was dried and concentrated. The residue was chromatographed on silica, eluting with cyclohexane:ethyl acetate (9:1). Evaporation of the appropriate fractions gave the title compound as a colourless oil (2.422g)

$[\alpha]_D$ -29.4° (c 1.36 MeOH)

Similarly prepared was:

Intermediate 47

[2R-(tert-Butyl-dimethyl-silanyloxy)-2-(3-chloro-phenyl)-ethylamino]-acetic acid methyl ester as a colourless oil (1.26g)

Assay: Found: C 56.9; H 7.95; N 3.9%

$C_{17}H_{28}ClNO_3Si$ requires C 57.1; H 7.8; N 3.9%

from amino-acetic acid methyl ester hydrochloride (1.05g) and (R)-(tert-butyl-dimethyl-silanoxy)-(3-chloro-phenyl)-acetaldehyde (2.16g).

Intermediate 48

{2R-(tert-Butoxycarbonyl)-[2R-(tert-Butyl-dimethyl-silanyloxy)-2-(3-chloro-phenyl)-ethyl]-amino}-propionic acid methyl ester

A mixture of 2R-[2R-(tert-Butyl-dimethyl-silanyloxy)-2-(3-chloro-phenyl)-ethylamino]-propionic acid methyl ester (2.149g) and di-t-butyl dicarbonate (1.37g) was heated at 80-100° for 1h. Chromatography of the residue on silica (50g) and elution with cyclohexane:ethyl acetate gave the title compound as a colourless oil (2.698g).

Assay: Found: C 58.4; H 8.1; N 3.0%

$C_{23}H_{38}ClNO_5Si$ requires C 58.5; H 8.1; N 3.0%

Similarly prepared was:

Intermediate 49

{(tert-Butoxycarbonyl)-[2R-(tert-Butyl-dimethyl-silanyloxy)-2-(3-chloro-phenyl)-ethyl]-amino}-acetic acid methyl ester as a colourless oil (1.55g) from [2R-(tert-Butyl-dimethyl-silanyloxy)-2-(3-chloro-phenyl)-ethylamino]-acetic acid methyl ester (1.20g)

$[\alpha]_D$ -25.2° (c 1.3 MeOH).

Intermediate 50

(6-Amino-pyridin-3-yl)-acetic acid methyl ester

A solution of (6-amino-pyridin-3-yl)-acetic acid (0.17g) in methanol (10ml) containing concentrated sulphuric acid (1ml) was stood at ambient temperature for 72h. The solution was partitioned between ethyl acetate and 2N sodium carbonate solution, and the phases separated. Further extraction of the aqueous phase with ethyl acetate, and concentration of the combined organic extracts gave the title compound as a dark green crystalline solid (0.131g)

$C_8H_{10}N_2O_2$: MH^+ 167

Intermediate 51

[2R-(tert-Butyl-dimethyl-silanyloxy)-2-(3-chloro-phenyl)-ethyl]-(1R-methyl-2-oxo-ethyl)-carbamic acid tert-butyl ester

1.5M di-isobutylaluminium hydride in toluene (8.1ml) was added dropwise to a stirred, cooled solution of the {2R-(tert-Butoxycarbonyl)-[2R-(tert-Butyl-dimethyl-silanyloxy)-2-(3-chloro-phenyl)-ethyl]-amino}-propionic acid methyl ester (2.296g) in toluene (50ml) at such a rate that the reaction temperature did not rise above -70°. The solution was stirred 1h at this temperature, then quenched with methanol (10ml). The mixture was preabsorbed on silica, evaporated, then chromatographed on silica eluting with

cyclohexane:ethyl acetate (9:1). Evaporation of appropriate fractions gave the title compound as a colourless oil (1.446g)

$C_{22}H_{36}ClNO_4Si$: MH^+ 443

Similarly prepared was:

Intermediate 52

[2R-(tert-Butyl-dimethyl-silanyloxy)-2-(3-chloro-phenyl)-ethyl]-(2-oxo-ethyl)-carbamic acid tert-butyl ester as a colourless gum (0.371g)

n.m.r. ($CDCl_3$): δ -0.15 (d, 3H), 0.05 (d, 3H), 0.90 (s, 9H), 1.45 (d, 9H), 2.9-3.2 (m, 1H), 3.4-3.65 (m, 1H), 3.70 (s, 3H), 3.75-4.15 (m, 2H), 4.8-5.0 (m, 1H), 7.05-7.35 (m, 4H).

from {(tert-Butoxycarbonyl)-[2R-(tert-Butyl-dimethyl-silanyloxy)-2-(3-chlorophenyl)-ethyl]-amino}-acetic acid methyl ester (0.500g).

Intermediate 53

(4-{2R-(tert-Butoxycarbonyl)-[2R-(tert-Butyl-dimethyl-silanyloxy)-2-(3-chloro-phenyl)-ethyl]-amino]-propylamino}-phenyl)-acetic acid ethyl ester

A solution of 2R-(tert-Butyl-dimethyl-silanyloxy)-2-(3-chloro-phenyl)-ethyl]-(1R-methyl-2-oxo-ethyl)-carbamic acid tert-butyl ester (1.119g) and 4-amino-phenylacetic acid ethyl ester (0.454g) in dichloromethane (30ml) containing acetic acid (0.29ml) was stirred for 1h, then treated with sodium triacetoxyborohydride (1.073g), and stirred a further 18h at room temperature. The mixture was washed with aqueous sodium bicarbonate solution, dried and concentrated. Chromatography of the residue on silica, elutiing with cyclohexane:ethyl acetate (4:1), and concentration of the appropriate fractions gave the title compound as a yellow oil (1.246g)

n.m.r. ($CDCl_3$): δ values include 1.38 (t, 3H), 1.57 (s, 9H),3.1-3.4 (m, 4H), 3.60 (s, 2H), 4.22 (q, 2H), 4.98-5.43 (broad d, 1H), 6.61 (d, 2H), 7.20 (d, 2H), 7.28-7.51 (m, 4H)

Similarly prepared were:

Intermediate 54

(5-{(tert-Butoxycarbonyl)-[2R-(tert-Butyl-dimethyl-silanyloxy)-2-(3-chloro-phenyl)-ethyl]-amino}-ethyl]-amino}-pyridin-2-yl)-acetic acid methyl ester as a yellow oil (0.317g)

$C_{29}H_{44}ClN_3O_5Si$: MH^+ 578

from [2R-(tert-Butyl-dimethyl-silanyloxy)-2-(3-chloro-phenyl)-ethyl]-(2-oxo-ethyl)-carbamic acid tert-butyl ester (0.360g) and methyl 5-aminopyridin-2-yl-acetic acid methyl ester (0.168g).

Intermediate 55

(6-{(tert-Butoxycarbonyl)-[2R-(tert-butyl-dimethyl-silanoxy)-2-(3-chloro-phenyl)-ethyl]-amino}-amino]-propylamino}-pyridin-3-yl)-acetic acid methyl ester as a pale yellow oil (0.105g)

$C_{30}H_{46}ClN_3O_5Si$: MH^+ 593

from [2R-(tert-butyl-dimethyl-silanoxy)-2-(3-chloro-phenyl)-ethyl]-(1R-methyl-2-oxo-ethyl)-carbamic acid tert-butyl ester (0.40g) and (2-amino-pyridin-5-yl)-acetic acid methyl ester (0.128g)

Intermediate 56

5-Amino-1H-pyrazole-3-acetic acid

A solution of 5-amino-3-cyanomethyl-1H-pyrazole-4-carbonitrile (5.0g) in 40% aqueous sodium hydroxide solution (60ml) was heated under reflux for 24h. The solution was cooled and acidified to pH 5.5 with concentrated hydrochloric acid. The resulting dark purple solution was evaporated to dryness, and the residue was extracted with ethanol. The extract was evaporated to give the title compound as a hygroscopic white solid (4.0g)

$C_5H_7N_3O_2$: MH^+ 142

Intermediate 57

(5-{(tert-Butoxycarbonyl)-[2R-(tert-butyl-dimethyl-silanoxy)-2-(3-chloro-phenyl)-ethyl]-amino}-amino]-propylamino}-pyrazol-3-yl)-acetic acid as a pale pink foam (0.061g)

$C_{27}H_{43}ClN_4O_5Si$: MH^+ 568

from [2R-(tert-butyl-dimethyl-silanoxy)-2-(3-chloro-phenyl)-ethyl]-(1R-methyl-2-oxo-ethyl)-carbamic acid tert-butyl ester (0.375g) and (5-amino-pyrazol-3-yl)-acetic acid (0.095g)

Example 1

(4-{2R-[2-(3-Chlorophenyl)-2R-hydroxy-ethylamino]propylamino}-phenyl)-acetic acid

(4-{2R-[2-(3-Chlorophenyl)-2R-hydroxy-ethylamino]propylamino}-phenyl)-acetic acid methyl ester (0.104g) in ethanol (1ml) was stirred with 2.5M aqueous sodium hydroxide solution (4ml) for 16h. The pH of the solution was adjusted to 8.0 and the solution was chromatographed on Amberlite XAD-2. The column was eluted with water, followed by ethanol:water (1:1). Concentration of the appropriate fractions followed by freeze-drying gave the title compound as a pale-brown solid (0.071g).

$C_{19}H_{24}ClN_2O_3$: MH^+ 363.1489 (to 3.7 ppm)

n.m.r. (D_2O): δ 1.25 (s, 3H), 3.07-3.42 (m, 7H), 4.90 (dd, 1H), 6.72 (d, 2H), 7.12 (d, 2H), 7.23-7.48 (m, 4H).

Example 2

[4-({2R-[2-(3-Chlorophenyl)-2R-hydroxy-ethylamino]-propyl}-methyl-amino)-phenyl]-acetic acid, sodium salt

A solution of [4-(2-Amino-propyl)-methyl-amino]phenylacetic acid, ethyl ester in dimethyl sulphoxide (1.5ml) was treated with N-trimethylsilylacetamide (0.069g), and the solution stirred under N_2 for 24h. A solution of (R)-3-chlorophenyloxirane (0.07g) in dimethylsulphoxide (0.25ml) was added and the mixture was heated at 65-75^o for 48h. The mixture was poured into 2N hydrochloric acid (25ml) and ethyl acetate (25ml), and the resultant mixture stirred vigorously for 1.5h. The phases

were separated, and the aqueous phase was extracted with ethyl acetate. The combined extracts were washed with brine, then dried and concentrated under reduced pressure. The residue was chromatographed on silica, eluting with 5% methanol in dichloromethane and concentration of the appropriate fractions gave an oil (0.12g). This was taken up in tetrahydrofuran (5ml) containing triethylamine (0.19ml),was treated with 1,1-carbonyl-di-imidazole (0.22g), and the mixture was stirred at room temperature for 24h. The mixture was concentrated, and the residue was chromatographed on silica, eluting with cyclohexane:ethyl acetate (3:1). Concentration of the appropriate fractions gave a pale yellow gum, (0.065g). This was dissolved in a mixture of ethanol (5ml) and 2.5M sodium hydroxide solution (4ml) and was heated under reflux for 16h. The solution was cooled, concentrated, and chromatographed on Amberlite XAD. The column was eluted with water, and the appropriate fractions were freeze-dried to give the title compound as a pale-brown solid (0.041g)

$C_{20}H_{26}ClN_2O_3$: MH^+ 377.163196 (error 2.8 ppm)

n.m.r (DMSO-d_6): δ values include 0.95 (d, 3H), 2.83 (s, 3H), 3.23 (s, 2H), 4.59 (t, 1H), 6.58 (d, 2H), 7.01 (d, 2H), 7.37 (s, 1H)

Example 3

(4-{2R-[2-(3-Chlorophenyl)-2R-hydroxy-ethylamino]propylamino}-phenyl)-acetic acid dihydrochloride

(4-{2R-[2R-(tert-Butyl-dimethyl-silanyloxy)-2-(3-chloro-phenyl)-ethylamino]-propylamino}-phenyl)-acetic acid ethyl ester (0.20g) was dissolved in tetrahydrofuran (3ml) and treated with 6M hydrochloric acid (3ml) for 18h at room temperature. The solution was evaporated to dryness, and the residue was dried *in vacuo* to give the title compound as a pale yellow foam (0.142g).

Assay: Found: C 50.3; H 5.7; N 6.1%

$C_{19}H_{23}ClN_2O_3.2HCl$ requires C 50.3; H 6.0; N 6.2%

n.m.r (DMSO-d_6): δ values include 1.32 (d, 3H), 2.9-3.6 (m, 3H), 3.48 (s, 2H), 5.00 (broad d, 1H), 6.59-7.10 (dd, 4H), 7.32-7.56 (dd, 4H)

Similarly prepared were:

Example 4

(3-{2R-[2-(3-Chlorophenyl)-2R-hydroxy-ethylamino]-propylamino}-phenyl)-acetic acid, dihydrochloride as an off-white solid (0.11g)

Assay: Found: C 51.45; H 5.9; N 6.3%

$C_{19}H_{23}ClN_2O_3.2HCl.0.5H_2O$ requires C 51.3; H 5.9; N 6.3%

n.m.r (DMSO-d_6): δ values include 1.41 (d, 3H), 3.67 (s, 2H), 5.02 (dd, 1H), 7.28 (t, 1H), 7.44 (s, 1H)

from (3-{2R-[2R-(tert-Butyl-dimethyl-silanyloxy)-2-(3-chloro-phenyl)-ethylamino]-propylamino}-phenyl)-acetic acid ethyl ester (0.24g):

Example 5

(4-{2R-[2-(3-Chlorophenyl)-2R-hydroxy-ethylamino]-2-methyl-propylamino}-phenyl)-acetic acid, dihydrochloride as a colourless foam (0.787g)

Assay: Found: C 53.8; H 6.4; N 6.2%

$C_{20}H_{24}ClN_2O_3.2HCl$ requires C 53.4; H 6.05; N 6.2%

n.m.r (DMSO-d_6): δ values include 1.35 (s, 6H), 2.90-3.25 (m, 2H), 3.35 (s, 2H), 3.40 (s, 2H), 5.05 (d, 1H), 6.70 (d, 2H), 7.00 (d, 2H), 7.30-7.50 (m, 4H)

from (4-{2-[2R-(tert-Butyl-dimethyl-silanyloxy)-2-(3-chloro-phenyl)-ethylamino]-methylpropylamino}-phenyl)-acetic acid ethyl ester (1.0g):

Example 6

(4-{2-[2-(3-Chlorophenyl)-2R-hydroxy-ethylamino]-ethylamino}-phenyl)-acetic acid, dihydrochloride

(4-{2-[2R-(tert-Butyl-dimethyl-silanyloxy)-2-(3-chloro-phenyl)-ethylamino]-ethylamino}-phenyl)-acetic acid ethyl ester (0.13g) was dissolved in tetrahydrofuran (5ml) and treated with 6M hydrochloric acid (5ml) for 68h at room temperature. The solution was evaporated to dryness, and the residue was dried *in vacuo* to give the title compound as colourless crystals (0.10g)

Assay: Found: C 49.5; H 5.6; N 6.3%

$C_{19}H_{23}ClN_2O_3.2HCl.0.75H_2O$ requires C 49.7; H 5.7; N 6.4%

n.m.r (DMSO-d_6): δ values include 3.42 (s, 2H), 5.02 (d, 1H), 6.70 (d, 2H), 7.04 (d, 2H), 7.46 (s, 1H)

Similarly prepared were:

Example 7

[4-({1-[2-(3-Chlorophenyl)-2R-hydroxy-ethylamino]-cyclopropylmethyl}-amino)-phenyl]-acetic acid as a yellow foam (0.426g)

$C_{20}H_{23}ClN_2O_3$: MH^+ 375.147547 (error 0 ppm)

n.m.r (DMSO-d_6): δ values include 0.84 (s, 2H), 1.11-1.32 (m, 2H), 5.02 (d, 1H), 6.68 (d, 2H), 7.00 (d, 2H), 7.32-7.51 (m, 4H)

from (4-{[1-(2R-(tert-Butyl-dimethyl-silanyloxy)-2-(3-chloro-phenyl)-ethylamino)-cyclopropylmethyl]-amino}-phenyl)-acetic acid methyl ester (0.412g):

Example 8

(4-{2R-[2-(3-Chlorophenyl)-2R-hydroxy-ethylamino]-3-methyl-butylamino}-phenyl)-acetic acid, dihydrochloride as an off-white solid (0.198g)

Assay: Found: C 53.1; H 6.3; N 5.6%

$C_{21}H_{29}ClN_2O_3.2HCl.0.5H_2O$ requires C 53.3; H 6.4; N 5.9%

n.m.r (DMSO-d_6): δ values include 1.02 (m, 6H), 2.21 (broad s, 1H) 3.05-3.45 (m, 5H), 5.09 (m, 1H), 6.65 (d, 2H), 7.05 (d, 2H), 7.30-7.50 (m, 4H)

from (4-{2-[2R-(tert-Butyl-dimethyl-silanyloxy)-2-(3-chloro-phenyl)-ethylamino]-3-methyl-butylamino}-phenyl)-acetic acid methyl ester (0.247g):

Example 9

[4-({2R-[2-(3-Chlorophenyl)-2R-hydroxy-ethyl}-methyl-amino)-phenyl]-acetic acid, dihydrochloride as a pale green solid (0.092g)

Assay: Found: C 49.3; H 6.1; N 6.05%

$C_{19}H_{23}ClN_2O_3.2HCl.1.5H_2O$ requires C 49.3; H 6.1; N 6.05%

n.m.r (DMSO-d_6): δ values include 2.90 (s, 2H), 3.00-3.30 (m, 2H), 3.70 (m, 1H), 5.05 (d, 1H), 6.85 (m, 2H), 7.15 (d, 2H), 7.20-7.50 (m, 4H)

from (4-{2-[2R-(tert-Butyl-dimethyl-silanyloxy)-2-(3-chloro-phenyl)-ethylamino]-ethyl)-methyl-amino}-phenyl)-acetic acid methyl ester (0.10g):

Example 10

[5-({1-[2-(3-Chlorophenyl)-2R-hydroxy-ethylamino]-cyclopropylmethyl}-amino)-pyridin-2-yl]-acetic acid dihydrochloride as a pale yellow foam (0.25g)

$C_{19}H_{22}ClN_3O_3$: MH^+ 376.142680 (error 0.3 ppm)

n.m.r (DMSO-d_6): δ values include 0.84 (s, 2H), 1.17-1.40 (m, 2H), 5.08 (d, 1H), 7.30-7.50 (m, 3H), 7.52 (s, 1H), 7.68 (d, 1H), 7.79 (dd, 1H), 8.14 (d, 1H)

from (5-[1-{2-[2R-(tert-Butyl-dimethyl-silanyloxy)-2-(3-chloro-phenyl)]-ethylamino} cyclopropylmethyl]-amino-pyridin-2-yl)-acetic acid methyl ester (0.258g):

Example 11

(5-{2R-[2-(3-Chlorophenyl)-2R-hydroxy-ethylamino]-propylamino}-pyridin-2-yl)-acetic acid, trihydrochloride as a brown solid (0.071g)

Assay: Found: C 46.2; H 5.7; N 8.6%

$C_{18}H_{22}ClN_3O_3.3HCl$ requires C 45.5; H 5.7; N 8.8%

n.m.r (DMSO-d_6): δ values include 1.27 (d, 3H), 4.00 (s, 2H), 5.12 (m,1H), 7.35-7.55 (m, 4H), 7.65 (d, 1H), 7.80 (dd, 1H), 8.25 (d, 1H)

from (5-{2R-[2R-(tert-Butyl-dimethyl-silanyloxy)-2-(3-chloro-phenyl)-ethylamino]-propylamino}-pyridin-2-yl)-acetic acid ethyl ester (0.102g);

Example 12

(2-{2R-[2-(3-Chlorophenyl)-2R-hydroxy-ethylamino]-propylamino}-thiazol-4-yl)-acetic acid, dihydrochloride as a pale brown solid (0.042g)

$C_{16}H_{22}ClN_3O_3S.2HCl$: MH^+ 370.099405 (error 0.5 ppm)

n.m.r (DMSO-d_6): δ values include 1.30 (d, 3H), 3.62 (s, 2H) 5.05 (m, 1H), 6.65 (s, 1H) 7.35-7.55 (m, 4H)

from (2-{2R-[2R-(tert-Butyl-dimethyl-silanyloxy)-2-(3-chloro-phenyl)-ethylamino]-propylamino}-thiazol-4-yl)-acetic acid ethyl ester (0.049g);

Example 13

5-{2R-[2-(3-Chlorophenyl)-2R-hydroxy-ethylamino]-propylamino}-benzo[1,3]dioxole-2-carboxylic acid, dihydrochloride as an off-white solid (0.301g)

Assay: Found: C 48.1; H 5.2; N 5.8%

$C_{19}H_{21}ClN_2O_3.2HCl.0.5H_2O$ requires C 48.1; H 5.1; N 5.9%

n.m.r (DMSO-d_6): δ values include 1.30 (s, 3H), 5.05 (m, 1H), 6.20 (d, 2H), 6.40 (s, 1H), 6.50 (s, 1H), 6.78 (d, 1H), 7.30-7.60 (m, 4H)

from (5-{2R-[2R-(tert-Butyl-dimethyl-silanyloxy)-2-(3-chloro-phenyl)-ethylamino]-propylamino}-benzo[1,3]dioxol-2-yl)-acetic acid methyl ester (0.342g):

Example 14

(5-{2-[2-(3-Chlorophenyl)-2R-hydroxy-ethylamino]-ethylamino}-pyridin-2-yl)-acetic acid, dihydrochloride

A solution of (5-{(tert-Butoxycarbonyl)-[2R-(tert-Butyl-dimethyl-silanyloxy)-2-(3-chloro-phenyl)-ethyl]-amino}-ethyl]-amino}-pyridin-2-yl)-acetic acid methyl ester (0.30g) in tetrahydrofuran (5ml) was treated with 6M hydrochloric acid (5ml) for 16h. The solution was evaporated to dryness to give the title compound as a pale yellow foam (0.146g)

Assay: Found: C 45.3; H 5.8; N 9.1%

$C_{17}H_{20}ClN_3O_3.2HCl.1.5H_2O$ requires C 45.9; H 5.2; N 9.15%

n.m.r (DMSO-d_6): δ values include 3.00-3.30 (m, 4H), 3.50-3.60 (m, 3H), 4.00 (s, 2H), 5.03 (d, 1H), 7.30-7.45 (m, 4H), 7.65 (d, 1H), 7.75 (dd, 1H), 8.18 (dd, 1H)

Similarly prepared were:

Example 15
(6-{2R-[2-(3-Chlorophenyl)-2R-hydroxy-ethylamino]-propylamino}-pyridin-3-yl)-acetic acid dihydrochloride as a pale yellow solid (0.074g)
$C_{18}H_{22}ClN_3O_3$: MH^+ 364.1435 (error 2ppm)
n.m.r. (DMSO-d6): δ values include 1.30 (d, 3H), 4.67 (m, 1H), 4.95 (m, 1H), 5.25 (m, 1H), 6.65 (d, 1H), 7.57 (d, 1H), 7.85 (s, 1H)
from (6-{(tert-Butoxycarbonyl)-[2R-(tert-butyl-dimethyl-silanoxy)-2-(3-chloro-phenyl)-ethyl]-amino]-amino]-propylamino}-pyridin-3-yl)-acetic acid methyl ester (0.102g).

Example 16
(5-{2R-[2-(3-Chlorophenyl)-2R-hydroxy-ethylamino]-propylamino}-pyrazol-3-yl)-acetic acid, dihydrochloride as a dark-red foam (0.044g)
$C_{16}H_{21}ClN_4O_3$: MH^+ 353.138219 (error 0.5 ppm)
n.m.r. (DMSO-d_6): d values include 1.27 (d, 3H), 5.06 (m, 1H), 7.05 (s, 1H), 7.27 (s, 1H), 7.33-7.52 (m, 3H)
from (5-{(tert-butoxycarbonyl)-[2R-(tert-butyl-dimethyl-silanoxy)-2-(3-chloro-phenyl)-ethyl]-amino]-amino]-propylamino}-pyrazol-3-yl)-acetic acid.

Example 17
(4-{2R-[2-(3-Chlorophenyl)-2R-hydroxy-ethylamino]propylamino}-phenyl)-acetic acid dihydrochloride as a colourless solid (0.035g)
from (4-{2R-(tert-Butoxycarbonyl)-[2R-(tert-Butyl-dimethyl-silanyloxy)-2-(3-chloro-phenyl)-ethyl]-amino]-propylamino}-phenyl)-acetic acid ethyl ester (0.047g).
Identical by n.m.r to the title compound of Example 3

The compound of intermediate 23 may also be considered to be an example of a physiologically acceptable derivative of compounds of formula (I)

TABLETS FOR ORAL ADMINISTRATION

Tablets may be prepared by the normal methods such as direct compression or wet granulation.

The tablets may be film coated with suitable film forming materials, such as hydroxypropyl methylcellulose, using standard techniques. Alternatively the tablets may be sugar coated.

Direct Compression Tablet

		mg/tablet
(i)	Active Ingredient	4.688
	Calcium Hydrogen Phosphate BP*	83.06
	Croscarmellose Sodium NF	1.8
	Magnesium Stearate BP	0.45
	Compression weight	90.0

* of a grade suitable for direct compression.

The active ingredient is passed through a 60 mesh sieve, blended with the calcium hydrogen phosphate, croscarmellose sodium and magnesium stearate. The resultant mix is compressed into tablets using a Manesty F3 tablet machine fitted with 5.5mm, flat bevelled edge punches.

		mg/tablet
(ii)	Active Ingredient.	0.31
	Anhydrous Lactose USNF	131.99
	Pregelatinised Starch USNF	7.0
	Magnesium Stearate BP	0.7

Compression weight	140.0

The active ingredient is passed through a 60 mesh sieve, and blended with the lactose, pregelatinised starch and magnesium stearate. The resultant mix is compressed into tablets using a Manesty F3 tablet machine fitted with 7.5mm normal concave punches.

SYRUP

This may be either a sucrose or sucrose free presentation.

A. Sucrose Syrup			mg/5ml dose
Active Ingredient			2.5
Sucrose BP			2750.0
Glycerine BP			500.0
Buffer	)		
Flavour	)		
Colour	)		as required
Preservative	)		
Purified Water BP		to	5.0ml

The active ingredient, buffer, flavour, colour and preservative are dissolved in some of the water and the glycerine is added. The remainder of the water is heated to dissolve the sucrose and is then cooled. The two solutions are combined, adjusted to volume and mixed. The syrup is clarified by filtration.

B. Sucrose-free Syrup	mg/5ml dose
Active Ingredient	2.5
Hydroxypropylmethylcellulose USP	

(viscosity type 4000)			22.5
Buffer	)		
Flavour	)		
Colour	)	as required	
Preservative	)		
Sweetener	)		
Purified Water BP		to	5.0ml

The hydroxypropylmethylcellulose is dispersed in hot water, cooled and then mixed with an aqueous solution containing the active ingredient and the other components of the formulation. The resultant solution is adjusted to volume and mixed. The syrup is clarified by filtration.

INJECTION FOR INTRAVENOUS ADMINISTRATION

		µg/ml
(i)	Active Ingredient	800
	Dilute Hydrochloric Acid BP to pH 3.5	
	Sodium Chloride Injection BP to 1ml	

The active ingredient is dissolved in a suitable volume of Sodium Chloride Injection BP, the pH of the resultant solution is adjusted to pH3.5 with dilute hydrochloric acid BP then the solution is made to volume with sodium chloride injection BP and thoroughly mixed. The solution is filled into Type I clear glass 5ml ampoules which are sealed under a headspace of air, by fusion of the glass then sterilised by autoclaving at 120^0 for not less than 15 minutes.

		µg/ml
(ii)	Active ingredient	56.2

Sodium Chloride BP	as required
Water for Injection BP to	1.0ml

Sodium chloride may be added to adjust the tonicity of the solution and the pH may be adjusted, using acid or alkali, to that of optimum stability and/or facilitate solution of the active ingredient. Alternatively, suitable buffer salts may be used.

The solution is prepared, clarified and filled into appropriate size ampoules sealed by fusion of the glass. The injection is sterilised by heating in an autoclave using one of the acceptable cycles. Alternatively, the solution may be sterilised by filtration and filled into sterile ampoules under aseptic conditions. The solution may be packed under an inert atmosphere of nitrogen or other suitable gas.

SUPPOSITORY FOR RECTAL ADMINISTRATION

Active ingredient		49.0 mg
Witepsol* H15	to	1.0g

*a proprietary grade of Adeps Solidus Ph.Eur.

A suspension of the active ingredient in molten Witepsol is prepared and filled using suitable machinery, into 1g size suppository moulds.

The compounds of Examples 1 and 11 were tested for beta-3-adrenoceptor activity using above described Methods 1 and 2 with the following results:

Test Method	EPMR	
	Example 1	Example 11
1	0.03	0.06
2	0.7	0.1

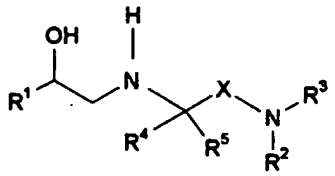
The protective effect of the compounds of Examples 1 and 11 was measured in above described Method 3 and ED_{50}'s of 0.07 and 0.001 mg/kg respectively were obtained.

Also carried out were tests for plasma glucose levels in mice as described by Bailey CJ and Flatt PR, *Textbook of Diabetes*, pp228-243, by Pickup JC and Williams G, (Blackwell Medical Publications,1991); and Largis EE et al, *Drug Development Research*, 32, 69-76, (1994) . In genetically diabetic (db/db) mice, the compound of Example 1 at a dose of 1mg/kg po for 7 days, caused a fall in plasma glucose levels of 422 mg/dl, compared to 784 mg/dl in control animals, (n=4)

No apparent adverse toxic effects were observed during the above *in vivo* tests due to the administration of the compounds of the invention.

CLAIMS

1. A compound of the general formula (I):



(I)

wherein

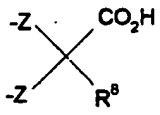
R^1 represents an aryl group optionally substituted by one or more substituents selected from halo, hydroxy, C_{1-6}alkoxy, C_{1-6}alkyl, nitro, cyano, hydroxymethyl and trifluoromethyl;

R^2 represents H or C_{1-6}alkyl;

R^3 represents a phenyl or heteroaryl group substituted by R^6 and R^7;

R^4 and R^5 each independently represent H or C_{1-6}alkyl or, R^4 and R^5 together form a C_{3-6} cycloalkyl group;

R^6 represents ZCH_2CO_2H and R^7 represents H or ZCH_2CO_2H, or R^6 and R^7 together represent a group



wherein each Z may be the same or different and is selected from a bond, CH_2, O, S or NR^9;

R^8 is H or CO_2H ;

R^9 is H or C_{1-6}alkyl;

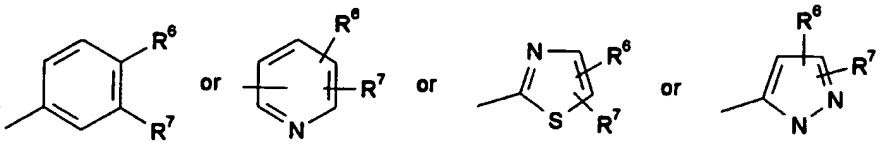
X represents $(CH_2)_n$ where n is 1 or 2;

and physiologically acceptable derivatives thereof.

2. A compound as claimed in claim 1 wherein R^1 represents a phenyl group substituted by a chlorine atom located in the meta position.

3. A compound as claimed in claim 1 or claim 2 wherein R^2 is methyl or H.

4. A compound as claimed in any one of claims 1 to 3 wherein R^3 represents a group

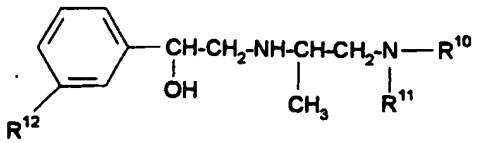


5. A compound as claimed in any one of claims 1 to 4 wherein R^4 and R^5 each independently represent H or C_{1-6}alkyl.

6. A compound as claimed in any one of claims 1 to 5 wherein X represents CH_2.

7. A compound as claimed in any one of claims 1 to 6 wherein R^6 represents ZCH_2CO_2H and R^7 represents H.

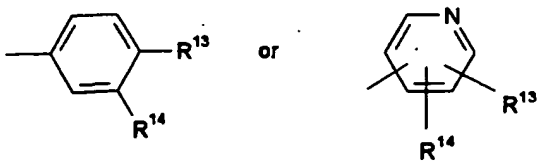
8. A compound as claimed in claim 1 wherein the compound of formula (I) is a compound of formula (II)



(II)

wherein

R^{10} represents



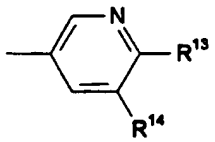
R^{11} represents H or C_{1-6}alkyl;

R^{12} represents a chlorine, fluorine or bromine atom or a methyl or trifluoromethyl group;

one of R^{13} and R^{14} represents H and the other of R^{13} and R^{14} represents CH_2CO_2H, $(CH_2)_2CO_2H$ or OCH_2CO_2H;

and physiologically acceptable derivatives thereof.

9. A compound according to any of claims 1 to 8 wherein R^3 or R^{10} represents



10. Compounds according to any of claims 1 to 9 which are;

(4-[2R-[2-(3-chlorophenyl)-2R-hydroxy-ethylamino]propylamino]-phenyl)-acetic acid;

(5-{2R-[2-(3-Chlorophenyl)-2R-hydroxy-ethylamino]-propylamino}-pyridin-2-yl)-acetic acid;

(4-{2-[2-(3-Chlorophenyl)-2R-hydroxy-ethylamino]-ethylamino}-phenyl)-acetic acid;

or physiologically acceptable derivatives thereof.

11. A compound according to any one of Claims 1 to 10 for use in therapy.

12. A method of treatment of a mammal, including man, suffering from a condition susceptible of amelioration by an atypical beta-adrenoceptor agonist comprising administration of an effective amount of a compound according to any one of claims 1 to 10 or a physiologically acceptable derivative thereof.

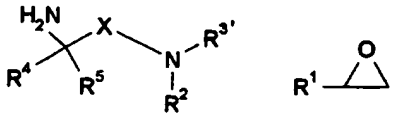
13. The use of a compound according to any one of claims 1 to 10 or a physiologically acceptable derivative thereof, for the manufacture of a medicament for the treatment of a condition susceptible of amelioration by an atypical beta-adrenoceptor agonist.

14. A pharmaceutical composition comprising a compound according to any one of claims 1 to 10 or a physiologically acceptable derivative thereof together with one or more pharmaceutically acceptable carriers.

15. A pharmaceutical composition which comprises a compound according to any one of claims 1 to 10 and a non-steroidal anti-inflammatory drug, together with one or more pharmaceutically acceptable carriers.

16. A process for preparing a compound of formula (I) as claimed in claim 1, or a physiologically acceptable derivative thereof which comprises:

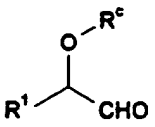
(A), reaction of a compound of formula (III) with a compound of formula (IV)



(III) (IV)

wherein $R^{3'}$ represents the group R^3 wherein the carboxylic acid moiety/moieties is/are protected;

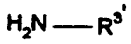
(B), reaction of a compound of formula (III) with a compound of formula (VII)



(VII)

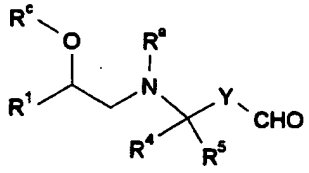
wherein R^c represents a protecting group, followed by reduction; or

(C), reaction of an amine of formula (VI)



(VI)

with a compound of formula (VIII)



(VIII)

wherein R^a represents a protecting group, followed by reduction;

followed by removal of any protecting groups present.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 95/02133

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D213/74 C07D277/42 C07D317/46 C07D231/38 C07C229/42 A61K31/44

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D C07C A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP,A,0 543 662 (SANKYO) 26 May 1993 cited in the application see page 3, line 36-41; claim 1 ---	1
Y	EP,A,0 565 317 (ZENECA) 13 October 1993 see the whole document ---	1
Y	EP,A,0 455 006 (AMERICAN CYANAMID) 6 November 1991 cited in the application see page 2, line 1-6 ---	1
A	US,A,4 154 761 (ALLEN & HANBURYS) 15 May 1979 see column 1-2 ---	1

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 September 1995	27. 09. 95

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Lauro, P

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Int. application No
PCT/EP 95/02133

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

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PCT/EP 95/02133

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PCT/EP 95/02133

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		JP-C- 1287917	14-11-85
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		JP-B- 60011898	28-03-85
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		SE-A- 7800930	04-08-78
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